Editor's Page

Complex Interrelationships Between Heart and Kidneys: Establishing the Role of Cardiorenal Syndrome

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The strong connection between renal and cardiovascular disease reflects the complex interactions between heart and kidneys. Arthur Guyton first extensively described normal physiological interactions between the control of extracellular fluid volume by the kidney and systemic circulation by the heart. However, the pathophysiological mechanisms underlying this reciprocal relationship between the heart and the kidneys are still ambiguous. A diseased heart has numerous adverse effects on kidney function, while in parallel, renal dysfunction can significantly impair cardiac function.[1] The so-called 'cardiorenal syndrome' is defined as a pathophysiological disorder of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ, This syndrome has recently been classified into 5 types.[2]

Type 1 cardiorenal syndrome is the most common and is characterized by a rapid worsening of cardiac function (pulmonary edema, acutely decompensated chronic heart failure, cardiogenic shock, and predominant right ventricular failure), leading to acute kidney dysfunction. In this setting, acute kidney injury is more severe in patients with impaired left ventricular ejection fraction compared with those with preserved left ventricular function, having an incidence >70% in patients with cardiogenic shock. Early diagnosis of acute kidney injury remains a challenge and novel biomarkers have shed light in this direction.

Neutrophil gelatinase-associated lipocalin (NGAL) appears to be one of the earliest markers detected in the blood and urine of humans with acute kidney injury in different clinical settings, including contrast-induced nephropathy. Notably, in these patients with acute renal dysfunction, an increase in creatinine levels is observed only 48 to 72 hours after detection of NGAL.[3] Furthermore, cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with chronic kidney disease, because its blood levels are not affected by age, gender, race, or muscle mass.[4] Cystatin C also predicts acute kidney injury at 12 hours, although NGAL outperformed cystatin C at earlier time points. Considering them together, they represent a combination of structural and functional damage to the kidney.

Type 2 (chronic) cardiorenal syndrome is characterized by chronic abnormalities in cardiac function causing progressive renal dysfunction, with a prevalence around 25%. Independent predictors of worsening renal function include old age, hypertension, diabetes mellitus, and acute coronary syndromes.[5] Hypoperfusion alone cannot explain the pathophysiology of renal dysfunction in this type of cardiorenal syndrome. The ESCAPE trial found a significant relation between right atrial pressure measured during pulmonary artery catheterization and serum creatinine, indicating the important role of renal congestion.[6]

Type 3 acute renocardiac syndrome, less common than type 1, is characterized by an abrupt and primary worsening of kidney function, leading to acute cardiac dysfunction (e.g. heart failure, arrhythmia, ischemia). Based on the RIFLE consensus definition (risk, injury, failure; loss; end-stage kidney disease), acute kidney injury has been identified in 9% of hospital patients and in 35% of ICU patients.[7] Mechanisms

underlying impairment of cardiac function through acute kidney injury include fluid overload leading to pulmonary edema, hyperkalemia causing arrhythmias, and uremia affecting myocardial contractility. Finally, renal ischemia itself may precipitate activation of inflammation and apoptosis at the cardiac level.[1]

Chronic renocardiac syndrome (type 4) is characterized by a condition of primary chronic kidney disease contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events. According to current diagnostic criteria for chronic kidney disease, at least 10% of the general adult population suffer from this major public health problem.[8]

More than 50% of deaths in end-stage renal disease cohorts are attributed to cardiovascular disease. In addition, patients with severe forms of chronic kidney disease have a 10- to 20-fold increased risk of cardiac death compared to the general population, while even less severe forms of chronic kidney disease may be associated with significant cardiovascular risk,[9] documenting an inverse relationship between renal function and adverse outcome (consistently occurring at estimated glomerular filtration rate levels <60 ml/min/1.73m^2). In this context, data derived from our institution show that parallel cardiac and renal involvement in hypertensive individuals without overt cardiovascular disease is associated with a very high risk of future cardiovascular events.[10] Part of this increased risk in patients with chronic kidney disease is attributed to under-treatment and less chance to receive risk-modifying interventions. Potential reasons for this sub-therapeutic performance include concerns about further worsening of renal function, and/or therapy-related toxic effects due to low clearance rates.[11]

Finally, secondary (type 5) cardiorenal syndrome is characterized by the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders. In the acute setting, severe sepsis represents the most common and serious condition that can affect both organs.

The depth of knowledge and complexity of care necessary to offer the best therapy to these patients demands a multidisciplinary approach, combining the expertise of cardiology, nephrology, and critical care, as was highlighted in the recent international symposium on "Renal dysfunction and cardiovascular diseases 2010" that took place in Athens. In conclusion, more attention needs to be paid to reducing risk factors for the cardiorenal syndrome. Under-treatment of the cardiorenal syndrome due to concerns about pharmacodynamics may have lethal consequences at an individual level and huge potential adverse consequences at a public health level.

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